**REMARKS**

Claim 22 is pending in the instant application. Claim 22 has been rejected. Reconsideration is respectfully requested in light of the following remarks.

**I. Priority**

In accordance with the Examiner's suggestion, Applicants have amended the specification as set forth above to recite priority under 35 USC 119 and 120 based upon previously filed applications.

**II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph Written Description**

Claim 22 has been rejected under 35 U.S.C. 112, first paragraph, because the subject matter is suggested to lack description in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. The Examiner suggests that the specification does not provide sufficient description of the chemical structure of PTP-1B inhibitors to demonstrate possession of the claimed invention at the time of filing.

Applicants respectfully disagree.

In order to identify the claimed inhibitor of PTP-1B, one would simply screen compounds against a preparation of PTP-1B. Not only is this approach well known to those skilled in the art, but the instant specification clearly describes how this can be accomplished. Further, the Examiner has acknowledged in the present office action, that one of skill in the art (prior to the filing of the instant application) would routinely be able to administer an inhibitor of the enzymatic activity of PTP-1B, see Office action dated 12/24/03 at page 12. Further yet, in this present office action at page 12, the Examiner acknowledges that one of skill would be motivated to test other various inhibitors of the enzymatic activity of PTP-1B. It is therefore respectfully pointed out that the Examiner should be estopped from asserting that it is **not** within the skill of one in the art to do so. Both of the prior art references (Ahmad and Puius) addressed in the following obviousness rejection are cited by the Examiner to show that one of skill could administer and routinely test for various inhibitors of PTP-1B. The references predate the priority date of the instant invention by several months and

thus, should be taken to represent the skill in the art at the time of filing.

Alternatively, the entire specification is directed to methods of identification of PTP-1B inhibitors. The specification describes a mouse model on pages 5-12. Based upon the results demonstrated by the knockout mouse of the present invention, inhibitors of the enzymatic activity of PTP-1B that will be useful in modulating the activity of the insulin receptor in living mammals for use in the treatment of obesity can be identified as described on page 12, lines 3-9; a method of identifying inhibitors of enzymatic activity of PTP-1B, as described on page 13, lines 3-11; a method of screening or identifying inhibitors of enzymatic activity of PTP-1B protein by transfecting a cell with DNA encoding the human PTP-1B protein, as described on page 13, lines 22-33; a method of determining whether a substance regulates obesity in a mammal, as described on page 16, lines 18 through page 18, line 25. Therefore, Applicants have **explicitly** taught how one of skill can identify and use inhibitors of PTP-1B.

Withdrawal of this rejection is respectfully requested.

**III. Rejection of Claims Under 35 U.S.C. 112, First Paragraph Enablement**

A. Specific Inhibitors

The Examiner has further rejected claim 22, as it is suggested that claim 22 contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and or use the invention. The Examiner suggests that the specification fails to provide teachings or guidance with particularity for any specific inhibitors that would be capable of treating obesity. Applicants respectfully disagree.

The enablement requirement as set forth in MPEP section 2164.01 requires that any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the

experimentation needed to practice the invention undue or unreasonable?

As further recited at MPEP section 2164, there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). In *Wands*, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The Court held that the

specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.*, 8 USPQ2d at 1407.

As set forth above, the present invention is drawn to a method of treating obesity comprising administering an inhibitor of the enzymatic activity of PTP-1B to an obese mammal. The present invention discloses a live animal model demonstrating both the effectiveness and lack of side effects of disrupting the PTP-1b gene. Prior to the instant invention, however, it was not known that PTP-1b would be a good target for therapeutic intervention. Both the effectiveness and lack of side effects of disrupting the PTP-1b gene were surprising and unexpected. Anyone skilled in the art would thus know that all inhibitors of PTP-1b would produce the same effect. Further, as a result of this invention being published, many investigators began programs

to discover new inhibitors using the approach described in the instant application. These potential inventors would not have been more convinced if the instant application had included a list of molecules that produce the claimed effect. As described above and acknowledged by the Examiner, it was well within the skill level of one in this art field to identify such inhibitors. Therefore, there would be no undue or unreasonable experimentation required to practice this invention.

Withdrawal of this rejection is respectfully requested.

B. Treatment of Obesity and Grievous Harm

The Examiner has further rejected claim 22 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of skill to make and use the invention. It is suggested that the specification does not provide teachings for administration of such inhibitors which would not cause grievous harm to an individual. Further, it is suggested that weight reduction is an unpredictable state of the art. It is suggested that it would require undue experimentation to make and use the invention.

Applicants respectfully disagree. MPEP §2107.03 states that it is improper for Office personnel to request evidence of safety

in the treatment of humans, or regarding the degree of effectiveness. See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

Therefore, Applicants respectfully submit that this is an improper rejection.

Further, contrary to the Examiner's suggestion, the specification clearly shows that the KO mouse has a remarkably normal phenotype, as supported throughout the specification and at page 12, lines 28-29. This normal phenotype is evidence that an inhibitor is not likely to cause grievous harm. The other actions of PTP-1b knockout or inhibition are either benign or serve to simply enhance the effects on obesity or diabetes. It would be readily apparent to one skilled in the art that administration of such inhibitors would not cause grievous harm to an individual.

Further there is no experimentation necessary to use the invention. Successful use of the present invention is clearly indicated by a weight loss in the patient.

The Examiner further argues that since obesity is both genetic and environmental, one could not predict that an inhibitor of PTP-1b would be effective in treating an obese mammal. This is not true. The instant application clearly shows that the KO animals given a high fat and carbohydrate diet are resistant to weight gain, see page 26 at line 31-page 27, line 5. Since this is an accepted model for predicting efficacy of drugs to treat obesity, the objections of the examiner are not relevant. Further, the mere fact that obesity is a multi-faceted disease should not be grounds for rejecting the claim. Many other diseases are also multi-faceted. For example, treatment of hypertension can be achieved with several different categories of drugs (alpha blockers, beta blockers, thiazide diuretics, loop diuretics, calcium blockers, ACE inhibitors). Treatment of hypertension is achieved by optimizing therapy with one or more of the above categories of drugs. The same is true for treating obesity with a PTP-1b inhibitor. For instance a patient can be treated with one or more anti-obesity drugs (including PTP-1b

inhibitors). The specification (particularly at Example 5) clearly shows that a PTP-1b KO animal that is fed a high fat and carbohydrate diet shows less weight gain than the wild-type animal fed the same diet. This result **clearly** supports that a human that is obese because of overeating would benefit from treatment with a PTP-1B inhibitor.

Withdrawal of these rejections under 35 U.S.C. §112, is therefore respectfully requested, in light of the foregoing arguments.

**IV. Rejection of Claim 22 Under 35 U.S.C. §112, Second Paragraph**

Claim 22 has been rejected Under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The claim is drawn to a method of treating obesity comprising administering an inhibitor of the enzymatic activity of PTP-1B to an obese mammal. The Examiner suggests that no clear and defined method steps are recited, specifically, it is unclear how administering an inhibitor of PTP-1B to an obese mammal relates to the preamble of the claim. Applicants respectfully disagree.

First, claim 22 is definite in that it sets forth the active positive step of administering an inhibitor of the enzymatic activity of PTP-1B to an obese mammal. While multiple steps are not recited, the claimed step is clear and defined. Claim 22 has been amended to clarify how administering an inhibitor of PTP-1B to an obese mammal relates to the preamble of the claim. Particularly claim 22 has been amended to recite a method of treating obesity comprising: identifying an inhibitor of the enzymatic activity of PTP1B and administering said inhibitor of the enzymatic activity of PTP-1B to an obese mammal wherein the inhibitor affects the regulation of the insulin receptor in the mammal so that a physiological weight loss is achieved in the mammal. Support for this amendment is found throughout the specification and at page 15, lines 15-23; page 18, lines 20-23, and pages 25-27. The scope of the invention as claimed cannot be considered to be vague or indefinite as all of the steps and terms of the claim are clearly taught in the specification.

Withdrawal of these rejections is respectfully requested.

**V. Rejection of Claim 22 Under 35 U.S.C. §103**

Claim 22 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Ahmad et al. in view of Puius et al. It is suggested that Ahmad teaches that obese human subjects have increased PTPase activity in their adipose tissue that can dephosphorylate and inactivate the insulin receptor kinase. It is further suggested that Ahmad teaches that PTPase activity was measured in the skeletal muscle of lean controls, insulin resistant obese non-diabetic subjects and obese subjects with non-insulin dependent diabetes. The Examiner suggests that Ahmad teaches that PTP-1B negatively regulates insulin receptor activation and since PTP-1B has a role in the negative regulation of insulin signaling and acts at least in part directly at the level of the receptor kinase, it may function in concert with LAR in the physiological regulation of the insulin receptor. It is acknowledged that Ahmad does not teach the inhibition of PTP-1B. It is further suggested that Puius teaches that PTPases have a sequence specificity that can be exploited in the design of potent and selective PTPase inhibitors, and further that PTP1B is implicated as a negative regulator of insulin stimulated pathways and the structure of PTP1B's active sites. It is suggested that

in view of the combined teachings it would have been obvious for one of skill in the art to administer an inhibitor of enzymatic activity of PTP-1B to an obese mammal to achieve weight loss. Further, it is suggested that one of skill would have been motivated to test various inhibitors of PTP-1B.

Applicants respectfully disagree. At the onset, it is respectfully pointed out that the priority date of the present invention is July 24, 1998. The publication date of the Puius reference is December 1997 or less than one year prior to the priority date of the present invention and as such it is an improper reference under 35 U.S.C. §103(a).

Further, to establish a *prima facie* case of obviousness under 35 U.S.C. §103(a), three basic criteria must be met, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both

be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). These criteria cannot be met by the recited art.

The present specification teaches that an inhibitor of PTP-1B is an effective drug for treating obesity. Neither of the prior art references, alone nor combined, teach that PTP-1B is a good target for any specific therapeutic intervention, and certainly not in the treatment of obesity.

Ahmad teaches *in vitro* muscle biopsy studies exploring changes in PTPase in skeletal muscle tissues. Contrary the Examiner's suggestion that that obese human subjects have increased PTPase activity in their adipose tissue that can dephosphorylate and inactivate the insulin receptor kinase, Ahmad actually teaches that two groups of obese subjects showed differing results related to the PTPase activity as compared to lean controls, see page 451, column 2. For example, one obese group experienced an increase in PTPase activity and one group experienced a decrease in PTPase activity. Therefore, this study can not possibly be construed to suggest that inhibiting enzymatic activity of PTP-1B in an obese animal will result in physiological weight loss. Ahmad does not teach all of the

limitations of claim 22, and thus can not be held to make obvious the present invention.

Further, as recited above Puius is an improper prior art reference and cannot be properly used to supply any teachings to the Ahmad reference under 103. However, even if Puius were deemed proper, it could be held to make obvious the present invention when combined with Ahmad. Puius simply teaches that PTPases work in concert with protein tyrosine kinases to regulate a vast array of cellular events including passage through the cell cycle proliferation and differentiation, metabolism, cytoskeletal organization, neuronal development and the immune response. Puius teaches that it may be possible to develop compounds that can simultaneously occupy the active site of PTP-1B and an adjacent non-catalytic site to gain higher affinity and selection. Puius does not teach or suggest that inhibiting PTP-1B would effect a reduction in weight nor that inhibiting PTP-1B would safely result in physiological weight loss in an obese mammal.

Thus the combination of Ahmad and Puius cannot be held to teach or suggest all of the claim limitations of the present invention.

Withdrawal of these rejections is therefore respectfully requested.

**VI. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claim is earnestly solicited.

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